Issues, Challenges, and Opportunities in Model-Based Drug Development for Monoclonal Antibodies

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ABSTRACT: Over the last two decades, there has been a simultaneous explosion in the levels of activity and capability in both monoclonal antibody (mAb) drug development and in the use of quantitative pharmacologic models to facilitate drug development. Both of these topics are currently areas of great interest to academia, the pharmaceutical and biotechnology industries, and to regulatory authorities. In this article, we summarize convergence of these two areas and discuss some of the current and historical applications of the use of mathematical-model-based techniques to facilitate the discovery and development of mAb therapeutics. We also consider some of the current issues and limitations in model-based antibody discovery/development and highlight areas of further opportunity. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2898–2908, 2013

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INTRODUCTION

Monoclonal antibodies (mAbs) and antibody-based therapeutics are a rapidly growing class of biotherapeutic agents. According to The Antibody Society,[1] as of June 2012, 34 mAbs have been approved, or are under review, in the European Union or the United States. Additionally, hundreds of antibodies are under study in various stages of drug development.[2] Given the considerable interest in antibody development, there is likewise a high level of interest in understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of antibodies. There are several comprehensive reviews of antibody PK and PD available,[2–5] as well as a number of reviews regarding specific aspects of antibody PK or PD.[6–12]

Interest in, and use of, quantitative pharmacologic models has also been rapidly growing in recent years, seemingly in parallel with the increased focus on mAb development. The types of quantitative models [e.g., indirect-response PK/PD models, physiologically based PK (PBPK) models, target-mediated drug disposition (TMDD) models, systems pharmacology models] that are applied to facilitate antibody development are certainly not unique to mAbs. However, there are specific attributes of mAbs that are unique relative to other therapeutics and that are particularly suited to specific quantitative approaches. Perhaps the most interesting of these attributes is the dichotomy of a shared "nonspecific" clearance (CL) mechanism (or, perhaps more properly termed, protective mechanism) across therapeutic antibodies in the neonatal Fc receptor (FcRn) pathway, combined with a highly specific, often capacity-limited target binding that is also often involved in the CL of mAbs. These characteristics make use of PBPK and TMDD models somewhat generalizable and potentially well suited for use in antibody development.

The intent of this commentary is not to provide a comprehensive review of antibody characteristics or of quantitative model-based approaches to therapeutic development. These topics have been reviewed previously, and references to detailed review articles are provided throughout the discussion. Rather, we hope to highlight how model-based development is currently being applied in the various phases of antibody drug development with representative examples, and discuss known issues and challenges to successful application. An overall summary for some of the major types of models is given in Table 1, with

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Table 1. Summary of Major Classes of Model-Based Approaches to Antibody Drug Development and Current Uses in Various Phases of Development

Model Type	Stage of Development	Major Utility
PK/PD models	Target identification through late-stage clinical	• Help assess importance of new targets • Help understand mAb characteristics for candidate optimization • Help translate to humans and design early clinical studies • Biomarker and clinical endpoint modeling to identify optimal clinical dosing regimens, important patient covariates, and potential target populations
Systems models	Target identification through late-stage clinical	• Evaluate importance of new targets • Evaluate new treatment options (e.g., treatment sequence or combination) • Inform dose selection in late-stage clinical development by predicting treatment effect from trial data in healthy subjects to target patient population • Integrate clinical endpoints with health outcomes measures
TMDD models	Candidate optimization through late-stage clinical	• Help understand mAb characteristics for candidate optimization • Human PK projection and starting dose range • Help determine optimal dose levels and dosing frequency in later clinical development
PBPK models	Candidate optimization through early-stage clinical	• Help understand mAb characteristics for candidate optimization • Human PK projection and starting dose range • Guidance on dose level/dose frequency in early clinical development for labeled mAbs

some of the advantages and disadvantages of these models summarized in Table 2. We also discuss further opportunities in this important arena.

DISCOVERY AND EARLY DEVELOPMENT

Application of model-based principles can be useful from the earliest stages of the antibody drug discovery/development process. Examples are available in the literature regarding the use of model-based approaches to facilitate target identification, to allow improved understanding of mechanism of action for a particular antibody and/or pathway, and to facilitate antibody engineering to allow drug candidate optimization. Examples of application of model-based approaches to facilitate discovery and early development, as well as some of the key issues and opportunities, are discussed below.

Target Identification

Perhaps the earliest use of quantitative pharmacologic models for drug development would be to assist in identification of optimal therapeutic targets. This can be performed by developing quantitative models to characterize a disease state (either an animal model or humans), and then using that model to look at the particular impact of intervening on a particular target or pathway in the overall treatment or disease. If the animal and mathematical models are sufficiently well characterized and predictive, this type of approach can help to identify the most promising therapeutic targets for a particular disease.

A few examples are available of quantitative modeling approaches that were developed to characterize animal models of disease to enable an understanding of the relative contribution of various potential targets within a disease state to the overall improvement of the disease condition. Examples include models developed to characterize experimental immune thrombocytopenia in rats[13] and mice,[14] both showing that significant improvements in individuals with this condition might be anticipated by developing therapies directed at the FcRn pathway that would lead to increased elimination of antiplatelet antibodies (e.g., antibody therapeutics directed at inhibiting binding of antiplatelet antibody to the protective FcRn receptor, thus increasing the CL of the pathogenic antibodies). Lon et al.[15] have also developed a quantitative model of collagen-induced arthritis in the rat, which was used to evaluate the mechanism of action of etanercept, and is positioned to evaluate the potential of other cytokine-blocking therapies to treat rheumatoid arthritis.

More extensive, multiscale systems pharmacology models have also been developed for a variety of disease states based on published clinical data. These